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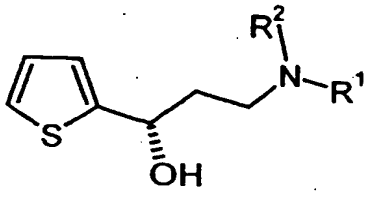
WO 2004/011452 A1

(54) Title: PROCESS FOR THE PREPARATION OF 3-HYDROXY-(2-THIENYL)PROPANAMINES

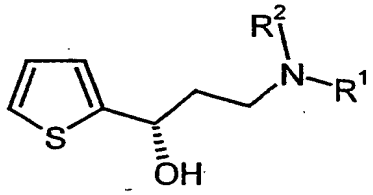


(I)

(57) Abstract: The present invention relates to a process for the preparation of compounds of the general formula (I) by catalytic enantioselective hydrogenation of the corresponding ketones. There are used inter alia ruthenium catalysts with chiral diamines and chiral biphosphines as ligands.

Process for the Preparation of 3-Hydroxy-(2-thienyl)propanamines

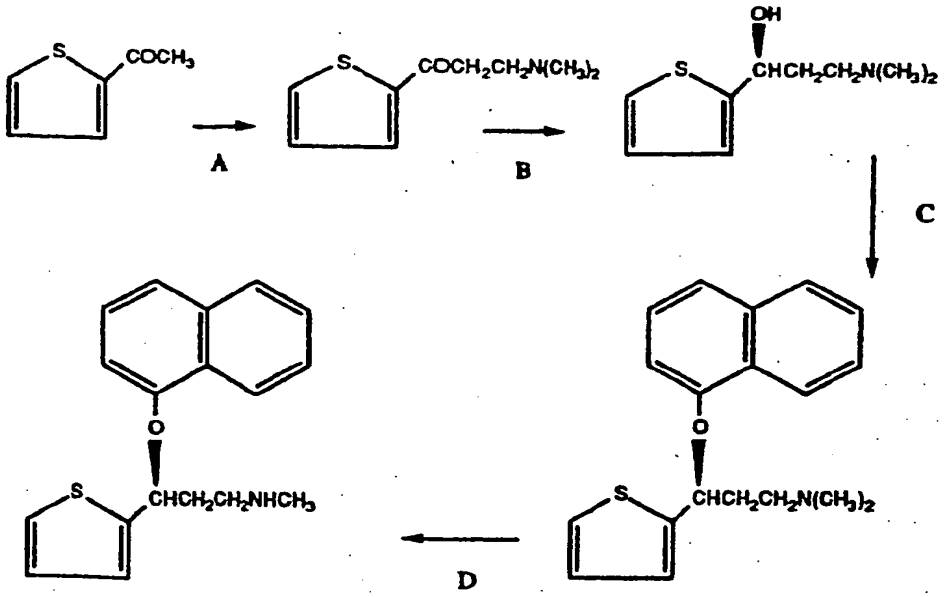
The present invention is directed to a process for the enantioselective hydrogenation of special α-heteroaryl ketones. In particular the invention relates to a process for the preparation of compounds of the general formula (I):



(I)

This class of compounds is used as intermediates for the synthesis of enantiomer-pure bioactive substances, e.g. Duloxetine®.

Duloxetine®, (S)-(+)-N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine hydrochloride, is a pharmaceutical that is used as an antidepressant and for the treatment of urinary incontinence. It inhibits the reuptake of both norepinephrine (?) and serotonin. The synthesis of Duloxetine® is described in detail in EP-A-273 658, EP-A-457 559 and EP-A-650 965.



Starting from 2-acetylthiophene, in stage A an aminomethylation is carried out with dimethylamine and formaldehyde (Mannich reaction). The 3-dimethylamino-1-(2-thienyl)-1-propanone that is formed is reduced in step B by means of complex hydrides to the corresponding alcohol 1-hydroxy-1-(2-thienyl)-3-dimethylaminopropane. The alcohol is then converted in step C with an alkali metal hydride and 1-fluoronaphathalene, optionally in the presence of a potassium compound (see EP-A-650 965), into the naphthyl derivate N,N-dimethyl-3-(1-naphthyloxy)-3-(2-thienyl)-propanamine. In the last step D the amino group is then demethylated by reaction with a chloroformic acid ester, preferably phenyl chloroformate or trichloroethyl chloroformate, optionally in the presence of a mixture of zinc and formic acid (EP-A-457 559), followed by alkaline hydrolysis of the carbamate to form N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine. The (S)-(+)-

enantiomer of the product in the hydrochloride form is the desired compound Duloxetine®.

Since a racemate is usually formed in the above synthesis of N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine, special measures are necessary for the selective preparation of the (S)-(+)-enantiomer. For example, EP-A-457 559 discloses an asymmetric reduction in step B by a complex of lithium aluminium hydride and a chiral ligand.

The disadvantage with the aforementioned synthesis pathway is in particular step D, i.e. the demethylation. In this connection highly corrosive chloroformic acid esters, optionally in combination with toxic zinc, are used in the last stage of the synthesis of a medicament, and carcinogenic methyl chloride is released. Complicated separation and purification steps consequently have to be subsequently employed. A conversion of the dimethylamino group into the desired monomethylamino group in an earlier synthesis stage would therefore be desirable. An alternative synthesis pathway for Duloxetine® would lead via the conversion of (S)-N-methyl-3-hydroxy-3-(2-thienyl)propanamine to (S)-(+)-N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine in the last step.

In EP-A-457 559 the enantioselective reduction of N-benzyl-N-methyl-1-(2-thienyl)-1-propanone to N-benzyl-N-methyl-3-(β-hydroxy)-3-(2-thienyl)propanamine is described in Example 1B. However, there is no indication of how N-methyl-N-benzyl-3-(β-hydroxy)-3-(2-thienyl)propanamine can be debenzylated. Investigations carried out by the inventors of the present application have shown that the conversion of N-methyl-N-benzyl-3-hydroxy-3-(2-

thienyl)propanamine with hydrogen in the presence of conventional palladium catalysts in solvents such as alcohols and acetic acid does not lead to the desired debenzylated monomethylamine N-methyl-3-hydroxy-3-(2-thienyl)propanamine.

Catalytic enantioselective hydrogenations of C=O double bonds have in the meantime become standard reactions in organic chemistry. For example GB2351735 discloses the use of certain catalysts in the reduction of special α-aryl methyl ketones. Reference is also made to the use of so-called diphosphine ligands in combination with ruthenium and a chiral diamine in the reduction of this substrate.

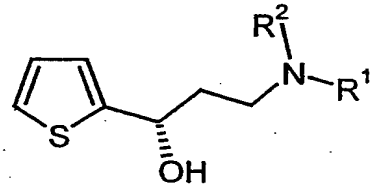
It has been found however that one specific catalyst or a class of catalysts cannot be used equally well in all hydrogenations, but that each reduction problem has to be investigated separately with regard to the catalyst use and the conditions. This is all the more so in the case of hydrogenations that take place with catalysts that consist not only of a ligand and a transition metal but that, as outlined in the above case, require two different ligands and the transition metal in order to be sufficiently active.

The object of the present invention was to provide a process for the enantioselective reduction of special α-heteroaryl ketones. This process should operate particularly well on an industrial scale having regard to economic and ecological aspects, i.e. should be superior to conventional methods of the prior art as regards space-time yield, enantiomer excesses, robustness and raw material costs or waste disposal costs. In particular the process should be suitable for providing in an advantageous manner

specific enantiomer-enriched alcohols as intermediates for the preparation of Duloxetine®.

This object is achieved according to the claims. Claim 1 is directed to the process according to the invention. Dependent subclaims describe preferred embodiments. Claim x is directed to a specific intermediate product formed in the present reduction.

Accordingly, in a process for the preparation of enantiomer-enriched compounds of the general formula (I)



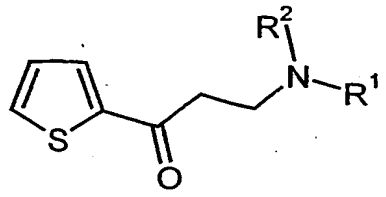
(I)

wherein

R^1 and R^2 independently of one another denote H, (C_1-C_8)-alkyl, (C_1-C_8)-acyl, (C_1-C_8)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl, (C_6-C_{18})-aryl, (C_7-C_{19})-aralkyl, (C_3-C_{18})-heteroaryl, (C_4-C_{19})-heteroaralkyl, $((C_1-C_8)\text{-alkyl})_{1-3}$-$(C_3-C_8)$-cycloalkyl, $((C_1-C_8)\text{-alkyl})_{1-3}$-$(C_6-C_{18})$-aryl, $((C_1-C_8)\text{-alkyl})_{1-3}$-$(C_3-C_{18})$-heteroaryl,

or the radicals R^1 and R^2 together form a (C_1-C_8)-alkylene bridge, wherein these may be substituted with one or more (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{18})-aryl, (C_7-C_{19})-aralkyl, (C_3-C_{18})-heteroaryl, (C_4-C_{19})-heteroaralkyl radicals with the formation of further chirality centres,

by enantioselective hydrogenation of compounds of the general formula (II)



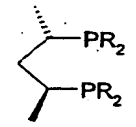
(II)

wherein R^1 and R^2 have the meanings given above, the aforementioned object is achieved especially advantageously according to the invention in a particularly surprising and in no way foreseeable manner by using for the hydrogenation a catalyst comprising an enantiomer-enriched bidentate phosphorus-containing ligand, a transition metal and a diamine, preferably a chiral diamine. Enantiomer-enriched alcohols of the general formula (I) can be prepared with the aid of these measures in very short reaction times and with high yields as well as excellent enantiomer excesses. It is particularly advantageous if in the above reaction compounds are used in which R^2 denotes a COR^1 group.

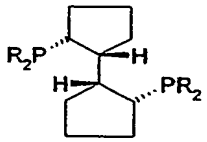
The term phosphorus-containing ligands is understood by the person skilled in the art to mean preferably bidentate biphosphines or biphosphites, or their mixed forms. Phosphite-containing ligands that may advantageously be used are described for example in J. Am Chem. Soc. 1994, 116, 4101; J. Org. Chem. 1997, 62, 6012; Asymmetry 10 (1999), 2129-2137; Asymmetry 10 (1999), 4009 or also in the supplement "Catalytic asymmetric synthesis", Iwao Ojima, Second Edition, Wiley-VCH 2000 and the literature cited therein. As biphosphine ligands there may be used the ligands mentioned in "Catalytic asymmetric synthesis", Iwao

Ojima, Second Edition, Wiley-VCH 2000. A further summary is published in ACS Symposium Series 641 "Reductions in Organic Synthesis, Chapter 2: Chiral Ruthenium(II)catalysts for Asymmetric Hydrogenation", 1996. An advantageous selection is shown in the following Scheme 1.

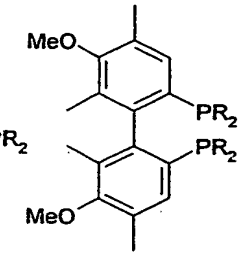
Scheme 1:



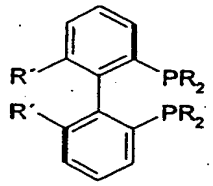
(S,S)-BDPP (SKEWPHOS)



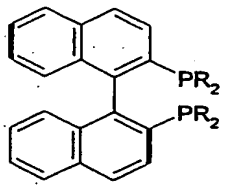
(R,R)-BICP



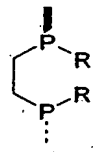
(R)-BIMOP



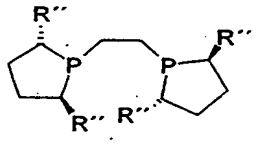
(R)-BIPHEMP



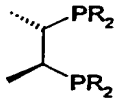
(R)-BINAP



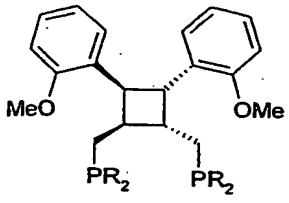
(R,R)-BisP



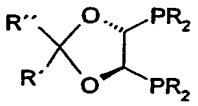
Me-BPE: R=Me
Et-BPE: R=Et
i-Pr-BPE: R=Me_2CH



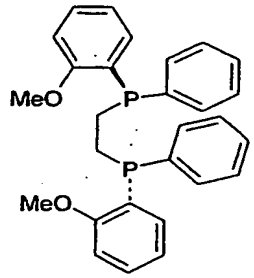
(S,S)-Chiraphos



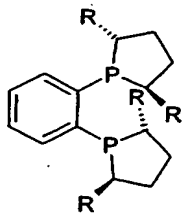
(R,R)-CDP



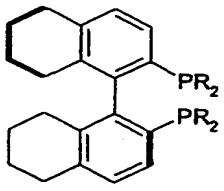
(S,S)-DIOP



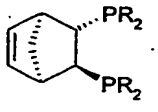
(S,S)-DIPAMP



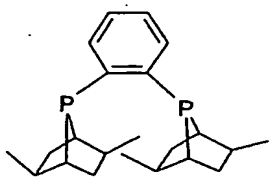
DuPhos



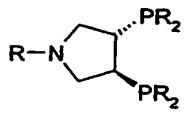
(R)-H_8-BINAP



(S,S)-NORPHOS



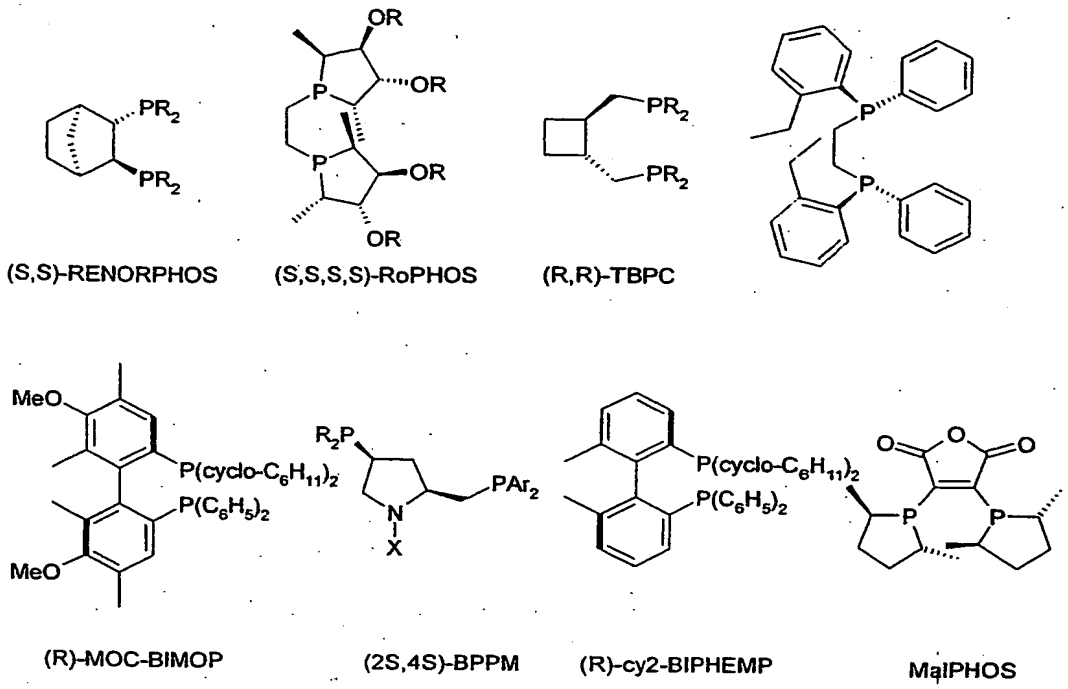
(R,S,R,S)-Me-PennPhos



(S,S)-Pyrphos (DEGUPHOS)

Further suitable compounds are shown in Scheme 2.

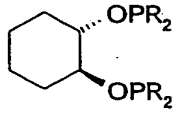
Scheme 2:



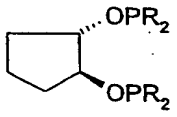
It is particularly advantageous to use chiral phosphorus-containing ligands selected from the group consisting of Deguphos, Binap, Phanephos, Norphos, DIOP, Duphos, Prophos, BDPP, BPPM, Malphos, Rophos or Basphos as described in Angew. Chem. 2001, 113, 40-75 and the literature cited therein; in J. Org. Chem. 1999, 64, 6907; in Synthesis 1997, 9, 983-1006 or in Org. Lett. Vol. 2, No. 12, 2000. The compounds disclosed in DE10100971 may also be used equally well.

Particularly suitable as phosphite ligands are the ligands shown in Scheme 3.

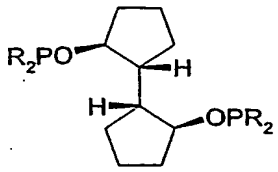
Scheme 3:



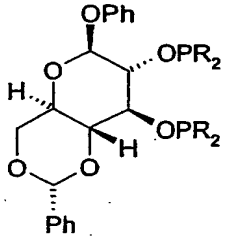
(S, S)-BDPCH



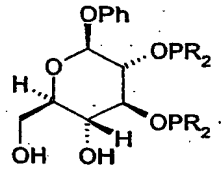
(S, S)-BDPCP



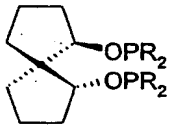
(S, S)-BICPO



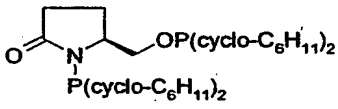
Ph-ß-GLUP



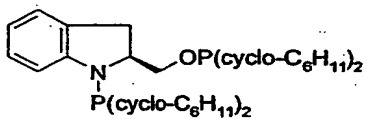
Ph-ß-GLUP-OH



(R,R,R)-spirOP



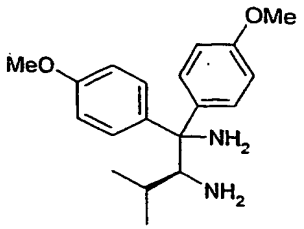
(S)-Cy, Cy-OxoProNOP



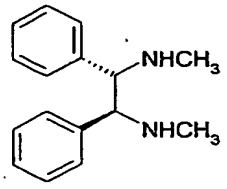
(S)-Cy, Cy-IndoNOP

As diamine there may in principle be used all chiral 1,2-diamine species that exhibit a sufficient activity or selectivity in the catalyst under consideration. Suitable diamines are in particular those mentioned in "Catalytic asymmetric synthesis", Iwao Ojima, Second Edition, Wiley-VCH 2000. A selection is shown in the following Scheme 4.

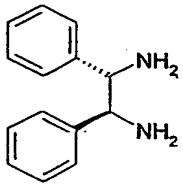
Scheme 4:



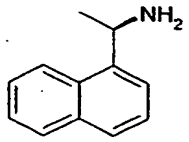
(S)-DAIPEN



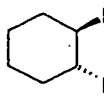
(S,S)-DMDPEN



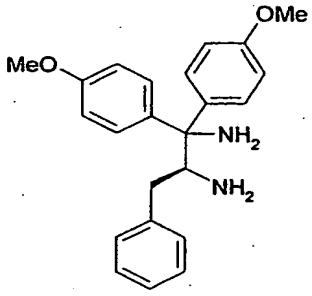
(S,S)-DPEN

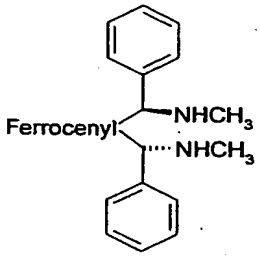


R-1-NEA



Cyclohexan-1,2-diamin

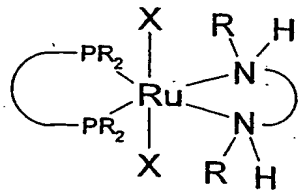




The use of chiral compounds selected from the group DAIPEN, DPEN, DMDPEN, 1,2-cyclohexyldiamine has proved particularly advantageous.

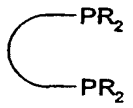
As transition metals there may in principle be used all transition metals that appear to the person skilled in the art to be suitable for the specific hydrogenation problem. In particular transition metals are selected from the group consisting of Ru, Rh, Ir, Pd, in any oxidation state that appears suitable for this purpose. Various counterions such as for example OTF^-, ClO_4^-, SbF_6^-, PF_6^- or BF_4^- or the like may be mixed for the purposes of charge equalisation with the overall complex of diamine, phosphine ligand and transition metal.

The advantageous catalyst resulting therefrom has the following structure V:



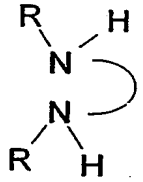
(V)

X is an anion as specified above, for achieving electrical neutrality. Preferred ligands of the general formula (VI)



(VI)

have as substituents R a (C_3-C_8)-cycloalkyl, (C_6-C_{18})-aryl, (C_7-C_{19})-aralkyl, methoxy-(C_7-C_{19})-aralkyl group, wherein the phosphane or phosphite groups are covalently bonded to a chiral carbon skeleton. The enantiomer-enriched amine ligands are represented by the general formula VII,



(VII)

wherein particularly suitable C2-symmetrical ligands, such as are listed in "Catalytic asymmetric synthesis", Iwao Ojima, Second Edition, Wiley-VCH 2000, may be employed.

The catalysts consisting of ligand/transition metal combinations and a corresponding diamine listed in the

following Table I are particularly suitable for the enantioselective hydrogenation of the ketone (II):

Table 1:

Phosphorus-Containing Catalyst	Diamine
(R)-Deguphos-RuCl2	1,2-ethylenediamine
(R)-Deguphos-RuCl2	(R, R)-DPEN
(R)-Deguphos-RuCl2	(R, R)-1,2-diaminocyclohexane
(R)-Deguphos-RuCl2	(R, R)-DAIPEN
(R)-BINAP*-RuCl2	1,2-ethylenediamine
(R)-BINAP*-RuCl2	(R, R)-DPEN
(R)-BINAP*-RuCl2	(R, R)-1,2-diaminocyclohexane
(R)-BINAP*-RuCl2	(R, R)-DAIPEN
(S)-DIOP-RuCl2	1,2-ethylenediamine
(S)-DIOP-RuCl2	(R, R)-DPEN
(S)-DIOP-RuCl2	(R, R)-1,2-diaminocyclohexane
(S)-DIOP-RuCl2	(R, R)-DAIPEN
(S)-PhanePHOS-RuCl2	1,2-ethylenediamine
(S)-PhanePHOS-RuCl2	(R, R)-DPEN
(S)-PhanePHOS-RuCl2	(R, R)-1,2-diaminocyclohexane
(S)-PhanePHOS-RuCl2	(R, R)-DAIPEN
(S)-BDPP-RuCl2	1,2-ethylenediamine
(S)-BDPP-RuCl2	(R, R)-DPEN
(S)-BDPP-RuCl2	(R, R)-1,2-diaminocyclohexane
(S)-BDPP-RuCl2	(R, R)-DAIPEN
(R)-Norphos-RuCl2	1,2-ethylenediamine
(R)-Norphos-RuCl2	(R, R)-DPEN
(R)-Norphos-RuCl2	(R, R)-1,2-diaminocyclohexane
(R)-Norphos-RuCl2	(R, R)-DAIPEN
(S,S)-BPPM-RuCl2	1,2-ethylenediamine

Phosphorus-Containing Catalyst	Diamine
(S,S)-BPPM-RuCl2	(R, R)-DPEN
(S,S)-BPPM-RuCl2	(R, R)-1,2-diaminocyclohexane
(S,S)-BPPM-RuCl2	(R, R)-DAIPEN
(R)-ProPhos-RuCl2	1,2-ethylenediamine
(R)-ProPhos-RuCl2	(R, R)-DPEN
(R)-ProPhos-RuCl2	(R, R)-1,2-diaminocyclohexane
(R)-ProPhos-RuCl2	(R, R)-DAIPEN

*) also includes TolBINAP and XylBINAP

The abbreviations of the ligand names as well as the graphic formulae of the ligands may be found in: Chemicals for Research, Catalog No. 19 from Strem, 2001-2003; Angew. Chem. 2001, 113, 40 [Lit. 16] or also in "Handbook of Chiral Chemicals", David J. Ager, Marcel Dekker Inc., 1999.

It is known to carry out enantioselective catalytic hydrogenations by two process variants that differ in principle (with molecular hydrogen or by transfer hydrogenation). Also, the process of the subject matter of the invention may be carried out either in the presence of molecular hydrogen or by means of transfer hydrogenation. Both types of process have been evaluated in the prior art and may be used analogously ("Asymmetric transferhydrogenation of C=O and C=N bonds", M. Wills et al. Tetrahedron: Asymmetry 1999, 10, 2045; "Asymmetric transfer hydrogenation catalysed by chiral ruthenium complexes", R. Noyori et al. Acc. Chem. Res. 1997, 30, 97; "Asymmetric catalysis in organic synthesis", R. Noyori, John Wiley & Sons, New York, 1994, p. 123; "Transition metals for organic Synthesis" Ed. M. Beller, C. Bolm, Wiley-VCH, Weinheim, 1998, Vol. 2, p. 97; "Comprehensive

Asymmetric Catalysis" Ed.: Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Springer-Verlag, 1999).

It has proved advantageous if a base is present in the reaction according to the invention. The use of a preferred base is governed by process technology and commercial considerations. The base should be as inexpensive as possible, but apart from this should be particularly effective and above all should not have any negative influence on for example the enantiomer purity of the products that are formed. In this connection alkali metal alcoholates are advantageous, such as for example sodium methanolate, sodium ethanolate or potassium tert.-butylate as well as potassium isopropylate or carbonates or hydroxides of alkali or alkaline earth metals. Also advantageous are organic nitrogen bases such as pyridine, DMAP, triethylamine, Hünig base, 1,2-ethylenediamine, diphenylenediamine, 1,2-di-(4-anisyl)-2-isobutyl-1,2-ethylenediamine and 1,2-di-(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

It is furthermore advantageous to use these bases in a sufficient amount. It has been found that acid residues obviously affect the present reaction in that on the one hand they lead to a low yield and on the other hand cause a low enantiomer enrichment of the products. The person skilled in the art is able to determine a suitably adequate excess of base. A molar excess of base referred to the catalyst used of >1000 : 1 is especially advantageous, an excess of > 100 : 1 being particularly preferred and an excess of > 20 : 1 being most particularly preferred. One of the bases mentioned above is accordingly added to the substrate in an amount of 10-50 %, particularly preferably 5-10 % and most particularly preferably 1-5 % referred to the latter.

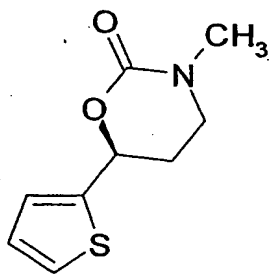
All solvents known to the person skilled in the art for this purpose may be used provided that they are inert with respect to the reaction according to the invention. In particular these are alcohols, advantageously the complementary alcohols of the alcoholates listed above, such as methanol, ethanol, isopropanol, tert.-butanol in their aqueous or non-aqueous form. The use of a mixture of isopropanol and potassium tert.-butylate is most particularly preferred.

The hydrogenation catalyst comprising the diamine, transition metal and the phosphorus-containing ligand is advantageously used in a concentration of 0.01-5 mole % referred to the substrate to be hydrogenated. It is particularly preferred to use the catalyst in a concentration that is as low as possible while ensuring the optimum possible conversion rate. The catalyst is particularly preferably used in a concentration of 0.1-1 mole %, and most particularly preferably in a concentration of 0.1-0.5 mole %.

The temperature during the reaction may in principle be chosen arbitrarily by the person skilled in the art as long as a sufficiently quick and selective reaction is guaranteed. The reaction is accordingly preferably carried out at temperatures between 0° and 100°C, more preferably between 10° and 80°C and particularly preferably between 20° and 60°C.

If the hydrogenation is carried out in the presence of molecular hydrogen, then a hydrogen pressure of 1-200, preferably 2-100 and particularly preferably between 5-80 bar should be adjusted.

The present invention also provides the cyclic carbamate of the formula III.



(III)

Depending on the reaction conditions, this may occur as a byproduct or main product in the hydrogenation of the corresponding carbamate-protected ketone (DE10207586), but may however advantageously be converted into the desired deprotected form by suitable hydrolysis.

In order to prepare the enantiomer-enriched N-methyl-3-(1-hydroxy)-3-(2-thienyl)propanamine the person skilled in the art proceeds by dissolving the corresponding ketone in an alcohol, adding the constituents of the hydrogenation catalyst to the mixture and then performing the hydrogenation at an appropriate temperature and suitable hydrogen pressure. Since the constituents of the hydrogenation catalyst (diamine, transition metal and phosphorus-containing ligand) may be used in several diastereomeric and enantiomeric forms and the complex formed in each case may therefore be present in so-called matched or mismatched configurations with regard to the substrate to be hydrogenated, the person skilled in the art must check which pair of enantiomer-enriched diamine and enantiomer-enriched phosphine ligand work most suitably in the hydrogenation catalyst. To prepare (S)-N-methyl-3-(1-hydroxy)-3-(2-thienyl)propanamine it has for example proved

suitable to use the (S)-PhanePhos-$RuCl_2$-(R,R)-DPEN complex as catalyst.

(C_1-C_8)-alkyl denotes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl, as well as all bond isomers.

(C_1-C_8)-alkoxy denotes a (C_1-C_8)-alkyl radical bound via an oxygen atom to the molecule in question.

(C_1-C_8)-acyl denotes a (C_1-C_8)-alkyl radical bound via a -C(=O) function to the molecule in question.

(C_1-C_8)-alkoxycarbonyl denotes a (C_1-C_8)-alkyl radical bound via a -O-C(=O) function to the molecule.

A (C_6-C_{18})-aryl radical is understood to denote an aromatic radical with 6 to 18 C atoms. This includes in particular species such as phenyl, naphthyl, anthryl, phenanthryl and biphenyl radicals. These may be substituted singly or multiply with (C_1-C_8)-alkoxy, (C_1-C_8)-haloalkyl, OH, Cl, NH_2, NO_2. Also, the radical may contain one or more heteroatoms such as N, O, S.

A (C_7-C_{19})-aralkyl radical is a (C_6-C_{18})-aryl radical bound via a (C_1-C_8)-alkyl radical to the molecule.

(C_1-C_8)-haloalkyl is a (C_1-C_8)-alkyl radical substituted with one or more halogen atoms. Suitable halogen atoms are in particular chlorine and fluorine.

A (C_3-C_{18})-heteroaryl radical denotes within the scope of the invention a five-membered, six-membered or seven-membered aromatic ring system of 3 to 18 C atoms that contains heteroatoms such as for example nitrogen, oxygen

or sulfur in the ring. Such heteroaromatics are in particular radicals such as 1-, 2-, 3-furyl, 1-, 2-, 3-pyrrolyl, 1-, 2-, 3-thienyl, 2-, 3-, 4-pyridyl, 2-, 3-, 4-, 5-, 6-, 7-indolyl, 3-, 4-, 5-pyrazolyl, 2-, 4-, 5-imidazolyl, acridinyl, chinolinyl, phenanthridinyl, 2-, 4-, 5-, 6-pyrimidinyl. These may be singly or multiply substituted with (C_1-C_8)-alkoxy, (C_1-C_8)-haloalkyl, OH, halogen, NH_2, NO_2, SH, S-(C_1-C_8)-alkyl.

A (C_4-C_{19})-heteroaralkyl is understood to denote an heteroaromatic system corresponding to the (C_7-C_{19})-aralkyl radical.

The expression (C_1-C_8)-alkylene bridge is understood to mean a (C_1-C_8)-alkyl radical that is bound via two different C atoms to the relevant molecule. This may be singly or multiply substituted with (C_1-C_8)-alkoxy, (C_1-C_8)-haloalkyl, OH, halogen, NH_2, NO_2, SH, S-(C_1-C_8)-alkyl or (C_6-C_{18})-aryl.

(C_3-C_8)-cycloalkyl is understood to denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl radicals. This may be singly or multiply substituted with (C_1-C_8)-alkoxy, (C_1-C_8)-haloalkyl, OH, halogen, NH_2, NO_2, SH, S-(C_1-C_8)-alkyl or (C_6-C_{18})-aryl.

Halogen is fluorine, chlorine, bromine or iodine.

The illustrated chemical structures relate to all possible stereoisomers that can be obtained by altering the configuration of the individual chiral centres, axes or planes, i.e. all possible diastereomers as well as all optical isomers (enantiomers) included therein.

Enantiomer-enriched or enantiomerically enriched denotes the presence in the mixture of an enantiomer in an amount of >50% compared to its optical antipode.

The specifications cited here are considered to be part of the disclosure. This application refers to the priority application DE10233724 which is herewith incorporated by referrence to its entirety. In particular it is referred to the disclosure of the usage of the Phanephos as ligand in present reaction. All the possibilities for residues R_2 or X^1 and X^2 mentioned in DE10233724 for compounds of formula (III) may be equally applied herein.

Example 1: (S)-3-N-ethoxycarbonyl-N-methylamino-1-(2-thienyl)-1-propanol

4.9 g (20.4 mmole) of 3-N-ethoxycarbonyl-N-methylamino-1-(2-thienyl)-1-propanone are added to a 100 ml Büchi stirred autoclave and the latter is evacuated. 18.4 mg (0.02 mmole) of (R)-TolBINAP-$RuCl_2$-(1R, 2R)-diphenylethylene-diamine are dissolved together with 0.4 ml (0.4 mmole) of a 1 M potassium tert.-butylate solution in 40 ml of isopropanol, stirred for 15 minutes, and sucked into the autoclave. After flushing with hydrogen, hydrogen is pumped in under a pressure of 10 bar and the mixture is hydrogenated for 2 hours at 40°C. The reaction mixture is filtered through Celite and concentrated by evaporation. 5.8 g of a yellowish-brown oil remain, which according to HPLC contains the desired alcohol in an enantiomer excess (ee) of 80.1 %. The conversion is > 96 %. After standing for a fairly long time, the content of cyclic carbamate (III) increases significantly.

^{1}H-NMR (DMSO-d^6): 1.15 (t,CH_3), 1.9 (m, CH_2), 2.85 (s, N-CH_3), 3.20 (m, CH_2), 4.0 (q, O-CH_2), 4.8 (m, CH), 5.65 (t, OH), 6.95 (m, 2H-arom.), 7.4 (m, 1H-arom.).

Example 2: (S)-[(N-methyl)-4-(2-thienyl)-tetrahydro-2H-oxazin-2-one (cyclic carbamate III).

50 g (207.4 mmole) of 3-N-ethoxycarbonyl-N-methylamino-1-(2-thienyl)-1-propanone are placed in a 1 l stirred autoclave which is then evacuated. 195 mg (0.2 mmole) of (R)-TolBINAP-$RuCl_2$-(1R, 2R)-diphenylethylenediamine are dissolved together with 2.2 ml (2.2 mmole) of a 1 M potassium tert.-butylate solution in 450 ml of isopropanol,

stirred for 15 minutes and sucked into the autoclave. After flushing with hydrogen, hydrogen is forced in under a pressure of 10 bar and the mixture is hydrogenated for 24 hours at 40°C. The reaction mixture is filtered through Celite and concentrated by evaporation. 52 g of a yellowish-brown oil remain, which slowly solidifies on standing. According to HPLC the oil contains the desired compound in an amount of > 80 %. 20 g of the crude product are stirred in isopropanol and suction filtered. The raw material is recrystallised from isopropanol. 6.7 g (34 %) of the cyclic carbamate were obtained.

^{1}H-NMR (DMSO-d^6): 2.18 (m, CH_2), 2.85 (s, N-CH_3), 3.35 (m, CH_2), 5.6 (dd, O-CH), 7.0 (m, 1H-arom.), 7.15 (m, 1H-arom.), 7.55 (m, 1H).

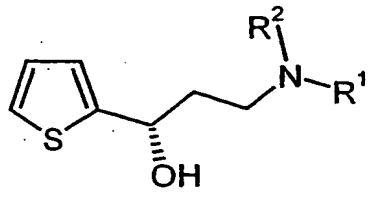
Example 3: 4.9 g (20.4 mmole) of 3-N-ethoxycarbonyl-N-methylamino-1-(2-thienyl)-1-propanone are placed in a 100 ml Büchi stirred autoclave, which is then evacuated. 4.9 mg (0.51 mmole) of (S)-PhanePhos-$RuCl_2$-(1R, 2R)-diphenylethylenediamine are dissolved together with 0.8 ml (0.8 mmole) of a 1 M potassium tert.-butylate solution in 40 ml of isopropanol, stirred for 15 minutes, and sucked into the autoclave. After flushing with hydrogen, hydrogen is forced in under a pressure of 10 bar and the reaction mixture is hydrogenated for 2 hours at 40°C. The reaction mixture is filtered through Celite and the filtrate is concentrated by evaporation. 4.1 g of a yellowish-brown oil remain, which according to HPLC has an ee of 93.4 %.

The monomethyl alcohol can be obtained according to a known procedure, which is described in application DE10207586, in

> 99 % ee from the enantiomer-enriched alcohol or cyclic carbamate after splitting off the protective groups.

Patent Claims:

1. Process for the preparation of enantiomer-enriched compounds of the general formula (I)

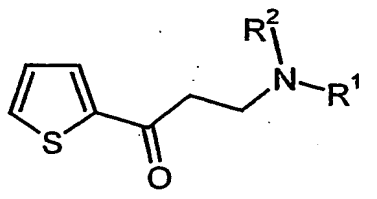


(I)

wherein

R^1 and R^2 independently of one another denote H, (C_1-C_8)-alkyl, (C_1-C_8)-acyl, (C_1-C_8)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl, (C_6-C_{18})-aryl, (C_7-C_{19})-aralkyl, (C_3-C_{18})-heteroaryl, (C_4-C_{19})-heteroaralkyl, $((C_1-C_8)$-alkyl$)_{1-3}$-(C_3-C_8)-cycloalkyl, $((C_1-C_8)$-alkyl$)_{1-3}$-(C_6-C_{18})-aryl, $((C_1-C_8)$-alkyl$)_{1-3}$-(C_3-C_{18})-heteroaryl, or the radicals R^1 and R^2 together form a (C_1-C_8)-alkylene bridge, wherein these may be substituted with one or more (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{18})-aryl, (C_7-C_{19})-aralkyl, (C_3-C_{18})-heteroaryl, (C_4-C_{19})-heteroaralkyl radicals with the formation of further chirality centres,

by enantioselective hydrogenation of compounds of the general formula (II)



(II)

wherein R^1 and R^2 have the meanings given above,

with a catalyst comprising an enantiomer-enriched bidentate phosphorus-containing ligand, a transition metal and a diamine.

2. Process according to claim 1, characterised in that chiral phosphorus-containing ligands are used selected from the group comprising Deguphos, Binap, Phanephos, Norphos, DIOP, Duphos, Prophos, BDPP, BPPM, Malphos, Rophos or Basphos.

3. Process according to claim 1, characterised in that as diamine a chiral compound is used selected from the group DIAPEN, DPEN, DMDPEN, 1,2-cyclohexyldiamine.

4. Process according to claim 1, characterised in that as transition metal a metal is used selected from the group comprising Ru, Rh, Ir, Pd.

5. Process according to one or more of the preceding claims, characterised in that hydrogenation is carried out in the presence of molecular hydrogen or by means of transfer hydrogenation.

6. Process according to one or more of the preceding claims, characterised in that the hydrogenation is carried out in the presence of a base.

7. Process according to claim 6, characterised in that the base is used in a molar amount of >10 : 1 referred to the catalyst.

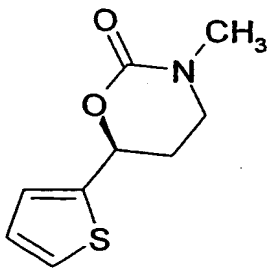
8. Process according to one or more of the preceding claims, characterised in that the hydrogenation is carried out in solvents selected from the group comprising methanol, ethanol, isopropanol, tert.-butanol in their aqueous or non-aqueous form.

9. Process according to one or more of the preceding claims, characterised in that the catalyst comprising the diamine, transition metal and the phosphorus-containing ligand is used in a concentration of 0.1-0.5 mole %.

10. Process according to one or more of the preceding claims, characterised in that the temperature during the hydrogenation is between 0° and 100°C, more preferably between 10° and 80°C and particularly preferably between 20° and 60°C.

11. Process according to one or more of the preceding claims, characterised in that in the case of hydrogenation with molecular hydrogen, a hydrogen pressure of 1-200, preferably 2-100 and particularly preferably between 5 and 80 bar is adjusted.

12. Cyclic carbamate of the formula III.



(III)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07927

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D333/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOYORI R., AT AL.: "General Asymmetric Hydrogenation of Hetero-aromatic Ketones" ORGANIC LETTERS, vol. 2, no. 12, 2000, pages 1749-1751, XP002255184 compounds (R,R)-2, 13, (S)-14, (S)-15 page 1751, column 2, line 10 - line 16; figure 1	1-12

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2003	06/10/2003

Name and mailing address of the ISA	Authorized officer
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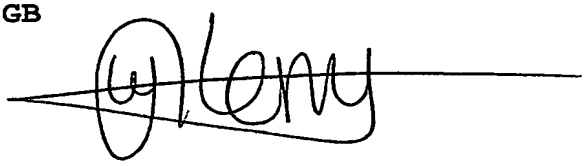
Form PCT/ISA/210 (second sheet) (July 1992)

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name:	HEMS, William
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Ely, United Kingdom
VIII-4-1-1-3	Mailing address:	29 Old Brewery Close
VIII-4-1-1-4	Citizenship:	GB
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	31st July 2003.

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VIII-4-1 -2-1	Name: 2-00	ROSSEN, Kai
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	Hanau, Germany DEX
VIII-4-1 -2-3	Mailing address:	Händelstrasse 3B
VIII-4-1 -2-4	Citizenship:	DE
VIII-4-1 -2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Kai Rossen
VIII-4-1 -2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	July 30, 2003
VIII-4-1 -3-1	Name: 3-00	REICHERT, Dietmar
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	Eschau, Germany DEX
VIII-4-1 -3-3	Mailing address:	Elsavastrasse 79
VIII-4-1 -3-4	Citizenship:	DE
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Dietmar Reichert
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	July 30, 2003

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VIII-4-1 -4-1	Name: 4.00	KÖHLER, Klaus
VIII-4-1 -4-2	Residence: (city and either US State, if applicable, or country)	Hainburg, Germany DEX
VIII-4-1 -4-3	Mailing address:	Kettelerstrasse 37
VIII-4-1 -4-4	Citizenship:	DE
VIII-4-1 -4-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Klaus Köhler
VIII-4-1 -4-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	July 30, 2003
VIII-4-1 -5-1	Name: 5.00	ALMENA PEREA, Juan José
VIII-4-1 -5-2	Residence: (city and either US State, if applicable, or country)	Hanau, Germany DEX
VIII-4-1 -5-3	Mailing address:	Friedrichstrasse 2d
VIII-4-1 -5-4	Citizenship:	ES
VIII-4-1 -5-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -5-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	JULY 31, 2003

 Fax Confirmation

020385 OC

PCT REQUEST

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0	For receiving Office use only	
0-1	International Application No.	PCT/EP 03/07927
0-2	International Filing Date	21 JUL 2003 (21.07.03)
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	020385 OC
I	Title of invention	PROCESS FOR THE PREPARATION OF 3-HYDROXY-(2-THIENYL) PROPANAMINES
II	Applicant	
II-1	This person is:	applicant only all designated States except US
II-2	Applicant for	
II-4	Name	DEGUSSA AG
II-5	Address:	Bennigsenplatz 1 D-40474 Düsseldorf Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	0 61 81 / 59-39 24
II-9	Facsimile No.	0 61 81 / 59-43 04
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor US only
III-1-2	Applicant for	
III-1-4	Name (LAST, First)	HEMS, William
III-1-5	Address:	29 Old Brewery Close Ely, Cambridgeshire CB7 4QE United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB

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III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ROSSEN, Kai
III-2-5	Address:	Händelstrasse 3B D-63452 Hanau Germany
III-2-6	State of nationality	DE
III-2-7	State of residence	DE
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	REICHERT, Dietmar
III-3-5	Address:	Elsavastrasse 79 D-63863 Eschau Germany
III-3-6	State of nationality	DE
III-3-7	State of residence	DE
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KÖHLER, Klaus
III-4-5	Address:	Kettelerstrasse 37 D-63512 Hainburg Germany
III-4-6	State of nationality	DE
III-4-7	State of residence	DE
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	ALMENA PEREA, Juan José
III-5-5	Address:	Friedrichstrasse 2d D-63450 Hanau Germany
III-5-6	State of nationality	ES
III-5-7	State of residence	DE

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	DEGUSSA AG
IV-1-2	Address:	Intellectual Property Management PATENTE und MARKEN Standort Hanau Postfach 13 45 D-63403 Hanau Germany
IV-1-3	Telephone No.	0 61 81 / 59-39 24
IV-1-4	Facsimile No.	0 61 81 / 59-43 04
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

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V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	24 July 2002 (24.07.2002)	
VI-1-2	Number	102 33 724.1	
VI-1-3	Country	DE	
VI-2	**Priority claim of earlier national application**		
VI-2-1	Filing date	11 December 2002 (11.12.2002)	
VI-2-2	Number	102 58 098.7	
VI-2-3	Country	DE	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	22	-
IX-3	Claims	3	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	31	

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	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney		-
IX-11	Copy of general power of attorney	reference no. AV 43529	-
IX-13	Priority document(s)	Item(s) VI-1, VI-2	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	Stef Retzow	
X-1-1	Name	DEGUSSA AG	
X-1-2	Name of signatory	i. V. Dr. Stefan Retzow	
X-1-3	Capacity	AV 43529	

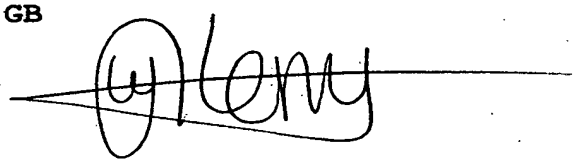
FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	21 JUL 2003	21.07.2003
10-2	Drawings:		
10-2-1	Received		
10-2-2	Not received		
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application		
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)		
10-5	International Searching Authority	ISA/EP	
10-6	Transmittal of search copy delayed until search fee is paid		

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to international application No. PCT/EP03/07927(if furnishing declaration pursuant to Rule 26ter) I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name:	HEMS, William
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Ely, United Kingdom
VIII-4-1-1-3	Mailing address:	29 Old Brewery Close
VIII-4-1-1-4	Citizenship:	GB
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	31st July 2003

VIII-4-1 -2-1	Name:	**ROSSEN, Kai**
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	**Hanau, Germany**
VIII-4-1 -2-3	Mailing address:	**Händelstrasse 3B**
VIII-4-1 -2-4	Citizenship:	**DE**
VIII-4-1 -2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 -3-1	Name:	**REICHERT, Dietmar**
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	**Eschau, Germany**
VIII-4-1 -3-3	Mailing address:	**Elsavastrasse 79**
VIII-4-1 -3-4	Citizenship:	**DE**
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1 -4-1	Name:	KÖHLER, Klaus
VIII-4-1 -4-2	Residence: (city and either US State, if applicable, or country)	Hainburg, Germany
VIII-4-1 -4-3	Mailing address:	Kettelerstrasse 37
VIII-4-1 -4-4	Citizenship:	DE
VIII-4-1 -4-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -4-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 -5-1	Name:	ALMENA PEREA, Juan José
VIII-4-1 -5-2	Residence: (city and either US State, if applicable, or country)	Hanau, Germany
VIII-4-1 -5-3	Mailing address:	Friedrichstrasse 2d
VIII-4-1 -5-4	Citizenship:	ES
VIII-4-1 -5-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -5-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	